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The multifunctional nuclear pore complex: a platform for controlling gene expression

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In addition to their established roles in nucleocytoplasmic transport, the intimate association of nuclear pore complexes (NPCs) with chromatin has long led to speculation that these structures influence peripheral chromatin structure and regulate gene expression. These ideas have their roots in morphological observations, however recent years have seen the identification of physical interactions between NPCs, chromatin, and the transcriptional machinery. Key insights into the molecular functions of specific NPC proteins have uncovered roles for these proteins in transcriptional activation and elongation, mRNA processing, as well as chromatin structure and localization. Here, we review recent studies that provide further molecular detail on the role of specific NPC components as distinct platforms for these chromatin dependent processes.

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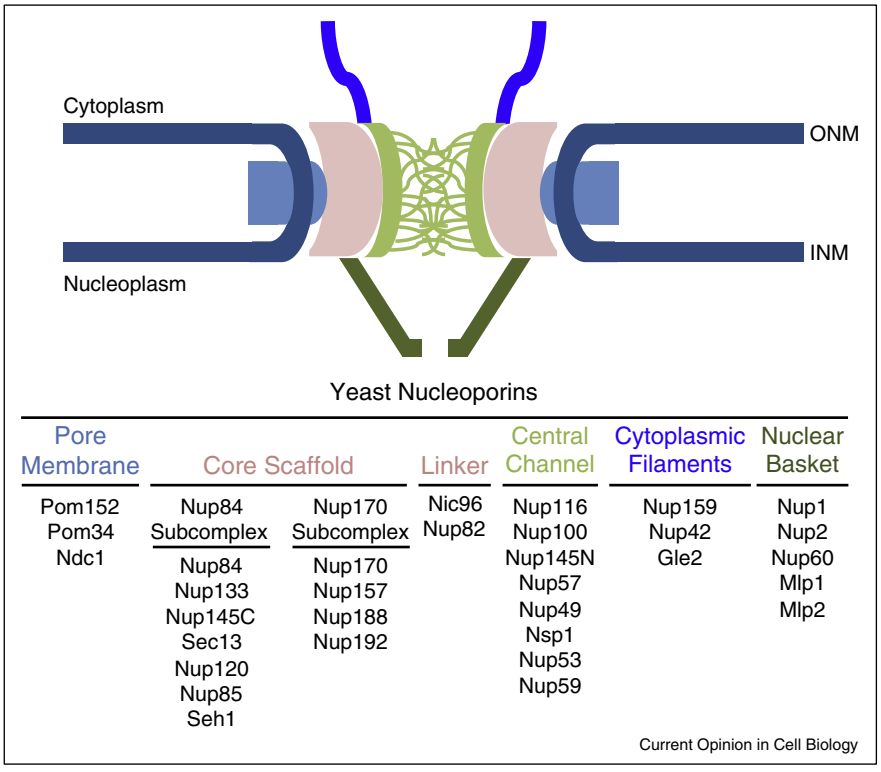
Introduction

Nuclear pore complexes (NPCs) perforate an otherwise impermeable nuclear envelope (NE) membrane and the primary function long ascribed to these channels is to regulate exchange of water-soluble metabolites and macromolecules between the cytoplasm and the nucleoplasm. NPCs are unlike other transport channels, both in their degree of complexity and the mechanisms by which they move a highly diverse array of cargos across the NE. Cylindrical in geometry, and ~60–100 million Daltons in mass, these evolutionarily conserved structures exhibit a distinguishing octagonal symmetry around a central transport channel. NPCs do not cross the two lipid bilayers of the NE, but rather they extend from the surface of the chromatin and penetrate the NE at pores formed where the inner and outer nuclear membranes are fused. The membrane walls of these pores are attached to the 'waists' of cylindrical NPCs (Figure 1) (reviewed in [1,2]).

Despite their large size and elaborate structure, NPCs are composed of relatively few proteins (~30). These nucleoporins (Nups) are present in multiple copies, and specific groups of Nups contribute to distinct repetitive subunits that assemble to form the NPC. On the basis of their structural features and localization within the NPC, Nups can be placed into distinct groups (Figure 1). Integral proteins of the pore membrane interact with complexes of Nups that form the core scaffold of the NPC, which includes the Nup84-subcomplexes and Nup170-subcomplexes. Multiple copies of these subcomplexes are organized into eightfold symmetrical ring structures that line the circumference of the pore where they interact with the pore membrane proteins and the membrane itself. Interestingly, sequence similarities between some Nups and coat proteins of secretory vesicles suggest these Nups have evolved from similar membrane coating ancestors. The core scaffold also supports Nups containing natively unfolded domains rich in phenylalanine-glycine (FG) residue repeats that occupy the central channel. These FG-Nups play a central role in transport. Among the FG-Nups, several members show a biased or strict localization to the nucleoplasmic or cytoplasmic face of the NPC. This group contributes to filaments that extend from the NPC core into the cytoplasm or nucleoplasm. In addition to FG-Nups, the nuclear fibers (a.k.a. nuclear basket) also consist of the proteins Mlp1 and Mlp2 (termed Tpr in vertebrates) (reviewed in [1,2]). Nuclear filaments likely play a role in transport, however, an accumulating body of data suggests these structures and other Nups exposed to the nucleoplasmic face of the NPC also play important roles in modulating chromatin structure and gene expression (reviewed in [3]).

In this review we summarize insights into the functional relationships between NPCs and the regulation of gene expression. It has long been speculated that NPCs are intimately associated with chromatin. Studies have underscored the importance of chromatin in NPC assembly, both in yeast and higher eukaryotes, including an intriguing requirement for chromatin remodeling factors in the assembly of yeast NPCs [4]. Conversely, observations continue to emerge showing the importance of Nups in chromatin structure and the regulation of gene expression. In this regard it is reasonable to view many Nups as chromatin-associated factors that act

Figure 1



Structural organization of NPCs. NPCs are embedded within the NE at sites where the outer nuclear membrane (ONM) and inner nuclear membrane (INM) are fused. NPCs are bound to the pore membrane through the integral pore membrane proteins and amphipathic domains of core Nups. The core scaffold Nups can be grouped into two subcomplexes, the Nup84p-subcomplexes and Nup170p-subcomplexes, which bind the linker Nup Nic96. The core scaffold contains multiple binding sites for the FG-containing Nups. The FG portions of these Nups are unstructured and fill the central channel. Filaments also extend from the NPC core into both the cytoplasm (cytoplasmic filaments) and nucleoplasm (nuclear basket).

within the context of the NPC platform to influence genome function.

NPCs associate with transcriptionally active and inactive chromatin

Chromatin is not randomly distributed within the nucleus. Each chromosome occupies a defined nuclear territory, and the chromatin therein localizes to specific spatial domains that are dependent upon distinct structural and functional states, including heterochromatin, which is highly compact and transcriptionally silent, and euchromatin, which is loosely packed and contains transcriptionally active loci [5]. Electron micrographs of nuclei from higher eukaryotes reveal that a portion of their heterochromatin is preferentially localized to the nuclear periphery, in close association with the nucleoplasmic face of the inner nuclear membrane (INM; Figure 2). This peripheral heterochromatic landscape, however, is disrupted at euchromatin channels that extend from NPCs into the nucleoplasm. It appears, at least in part, that these euchromatin channels are maintained by components of the NPC nuclear basket including Tpr in metazoan cells [6]. The association of NPCs with euchromatin has long been interpreted to reflect their association with transcriptionally active genes [7].

Chromatin organization in the yeast *Saccharomyces cerevisiae* shows many similarities to higher eukaryotes, providing a genetically tractable model organism for such studies (reviewed in [8]). Many regions of silenced chromatin reside primarily at the nuclear periphery, including telomeric and subtelomeric chromatin, centromeres, and silenced mating loci, and the basket components Mlp1/2 are implicated in keeping NPCs free from heterochromatin crowding [9••]. By contrast, numerous actively transcribing genes are observed to associate with NPCs. These active genes interact with Nups present in disparate substructures of the NPC, including the nuclear basket, the core scaffold, and the central channel. Interestingly, NPCs are also associated with silenced chromatin and studies suggest that NPCs function in the deposition of these chromatin domains adjacent to the INM. This myriad of interactions suggests NPCs possess